Notice of Allowability	Application No.	Applicant(s)	
	10/734,661	YAYON ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/18/2008*.

2. ☒ The allowed claim(s) is/are *1,10,31 and 50-52*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9/3/08
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20080909* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

Examiner's Amendment

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 20, 2008, has been entered.

2. The amendment filed May 20, 2008, is acknowledged and has been entered. Claims 1, 7, 8 and 10 have been amended. Claims 6, 9, 15, 18, 20 and 22 have been cancelled.

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for entry of this examiner's amendment was given by Applicant's Representative, Allan Fanucci on September 9, 2008.

Response to Amendment

4. The previously filed amendments to the specification which only identify the amendments to be made by referring to the published application are considered non-compliant because these amendments fail to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611,* Jun. 30, 2003). In this case, the amendments are non-complaint because the published application is not considered part of the specification and 37 CFR § 1.121 requires that amendments be made by

identifying the location in the specification where the amendments are to be made. (see 37 CFR § 1.121(b)).

However, in order resolve this issue, rather than mailing a Notice of Non-Compliant Amendment, the Examiner contacted Applicant's representative, Allan Fanucci and requested that Applicant provide the location in the substitute specification filed 6/7/2004 of the amendments previously filed. Mr. Fanucci provided these locations as detailed in the below amendments to the specification. Therefore, in order to expedite the allowance of the application the specification amendments have been entered by Examiner's amendment.

5. The application has been amended as follows:

In the claims:

The prior set of claims has been replaced by the following set of claims:

1. (Currently Amended) ~~A molecule comprising the antigen-binding portion of an~~ An isolated antibody or antigen-binding fragment thereof, wherein said antibody or said antigen-binding fragment thereof ~~which~~ specifically binds ~~and blocks ligand-independent activation of a~~ the extracellular domain of the human fibroblast growth factor receptor 3 (FGFR3) ~~having an extracellular portion which is encoded by SEQ ID NO: 4~~ polypeptide comprising the amino acid sequence of SEQ ID NO:1 and wherein said antibody or said antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:95.

Claims 2-9. (Cancelled)

10. (Currently Amended) A ~~pharmaceutical~~ composition [[,]] comprising ~~as an active ingredient at least one~~ the antibody or antigen-binding fragment thereof ~~molecule~~ according to claim 1 ~~and a pharmaceutically acceptable carrier, excipient, or auxiliary agent~~.

Claims 11-30. (Cancelled)

31. (Currently Amended) A kit comprising the antibody or antigen-binding fragment thereof ~~molecule of~~ claim 1~~, at least one reagent suitable for detecting the presence of said molecule when bound to said FGFR3 and instructions for use~~.

Claims 32-49. (Cancelled)

50. (New) An isolated antibody or antigen-binding fragment thereof, wherein said antibody or said antigen-binding fragment thereof specifically binds the extracellular domain of the human fibroblast growth factor receptor 3 (FGFR3) polypeptide comprising the amino acid sequence of SEQ ID NO:1 and wherein said antibody or said antigen-binding fragment thereof comprises a heavy chain variable region comprising the 3 complementarity determining region (CDR) amino acid sequences of the heavy chain variable region amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the 3 CDR amino acid sequences of the light chain variable region amino acid sequence of SEQ ID NO:95.

51. (New) A composition comprising the antibody or antigen-binding fragment thereof according to claim 50.

52. (New) A kit comprising the antibody or antigen-binding fragment thereof of claim 50.

In the specification:

The specification has been amended as follows:

Please amend the paragraph starting at page 7, line 15 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Another currently preferred embodiment of the present invention provides a molecule herein denoted MSPRO12 comprising a variable light chain (V_L) having SEQ ID NO:[[94]] 87 and a variable heavy chain (V_H) having amino acid SEQ ID NO:[[105]] 98 and the corresponding isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[75]] 68 and SEQ ID NO:[[89]] 82, respectively. - -

Please amend the paragraph starting at page 7, line 20 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Another currently preferred embodiment of the present invention provides a molecule herein denoted MSPRO2 comprising a variable light chain (V_L) having SEQ ID NO:[[92]] 85 and a variable heavy chain (V_H) having SEQ ID NO:[[103]] 96 and the corresponding isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[74]] 67 and SEQ ID NO:[[84]] 77. - -

Please amend the paragraph starting at page 7, line 24 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - A currently most preferred embodiment of the present invention provides a molecule, herein denoted MSPRO59, comprising a variable light chain (V_L) having SEQ ID NO:[[102]] 95 and a variable heavy chain (V_H) having SEQ ID NO:[[113]] 106 having the corresponding

isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[76]] 69 and SEQ ID NO:[[91]] 84, respectively. - -

Please amend the paragraph starting at page 8, line 4 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - In one embodiment the present invention provides a molecule which binds FGFR3 and blocks ligand-dependent activation of the receptor, comprising V_H-CDR3 and V_L-CDR3 regions having SEQ ID NO:20 and SEQ ID NO:21, respectively and the corresponding polynucleotide sequence having SEQ ID NO:44 and SEQ ID NO:45, respectively. In another embodiment the present invention provides a molecule comprising a variable light chain (V_L) having SEQ ID NO:[[99]] 92 and a variable heavy chain (V_H) having SEQ ID NO:[[110]] 103, having the corresponding isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[65]] 58 and SEQ ID NO:[[87]] 80, respectively. - -

Please amend the paragraph starting at page 8, line 18 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Additional embodiments of the present invention provide molecules having an antigen binding domain comprising a V_L region and a V_H region, respectively, selected from SEQ ID NO:[[93]] 86 and SEQ ID NO:[[104]] 97; SEQ ID NO:[[95]] 88 and SEQ ID NO:[[106]] 99; SEQ ID NO: [[96]]89 and SEQ ID NO:[[107]] 100; SEQ ID NO:[[97]] 90 and SEQ ID NO:[[108]] 101; SEQ ID NO:[[98]] 91 and SEQ ID NO:[[109]] 102; SEQ ID NO:[[99]] 92 and SEQ ID NO:[[110]] 103; and SEQ ID NO:[[101]] 94 and SEQ ID NO:[[112]] 105 and the corresponding isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[70]] 63 and SEQ ID NO:[[85]] 78; SEQ ID NO:[[67]] 60 and SEQ ID NO:[[78]] 71; SEQ ID NO [[64]]57 and SEQ ID NO:[[79]] 72; SEQ ID NO:[[71]] 64 and SEQ ID NO:[[86]] 79; SEQ ID NO:[[62]] 55 and SEQ ID NO:[[80]] 73; SEQ ID NO:[[65]] 58 and SEQ ID NO:[[87]] 80; and SEQ ID NO:[[69]] 62 and SEQ ID NO:[[83]] 76. - -

Please amend the paragraph starting at page 8, line 31 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Another embodiment of the present invention provides a molecule comprising V_H and V_L domains of amino acid sequences having SEQ ID NO:[[111]] 104 and [[100]] 93, which has specific affinity for FGFR1 and which blocks ligand-dependent activation of FGFR1, and the corresponding isolated nucleic acid molecules comprising polynucleotide sequences having SEQ ID NO:[[82]] 75 and SEQ ID NO:[[73]] 66. - -

Please amend the paragraph starting at page 11, line 9 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - ~~Figures 9A-9D~~ **FIG. 9** demonstrates the specificity and potency of MS-PRO Fabs by Western blot with anti-P-ERK (phosphorylated/activated ERK) antibody. **FIG. 9A** shows a dose response of MSPRO 29, 59 and 54 on RCJ-M14 cells. **FIG. 9B** shows a dose response of MSPRO 29, 59 and 54 on RCJ-W11 cells. **FIG. 9C** shows a dose response of MSPRO 29, 59 and 54 on RCJ-R1-1 cells. **FIG. 9D** shows a dose response of MSPRO 29, 59 and 54 on RCJ-R2-2 cells. - -

Please amend the paragraph starting at page 11, line 23 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - ~~Figures 16A-16D~~ **FIG. 16** shows the selective binding of radiolabeled MSPRO29 to histological sections of growth plate. **FIG. 16A** shows Hematoxylin-cosin staining of growth plate treated with radiolabeled MSPRO29 at x100 magnification. **FIG. 16B** shows radiomicroscopic sections of growth plate treated with radiolabeled MSPRO29 at x100 magnification. **FIG. 16C** shows radiomicroscopic sections of growth plate treated with radiolabeled MSPRO29 at x400 magnification. **FIG. 16D** shows Hematoxylin-cosin staining of growth plate treated with radiolabeled Ly6.3 at x100 magnification. **FIG. 16E** shows

radiomicroscopic sections of growth plate treated with radiolabeled Ly6.3 at x100 magnification. **FIG. 16F** shows radiomicroscopic sections of growth plate treated with radiolabeled Ly6.3 at x400 magnification. - -

Please amend the paragraph starting at page 12, line 12 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Figure 28 is an example of a Fab expression vector, having SEQ ID NO:[[53]] 52, for use in accordance with the present invention. - -

Please amend the paragraph starting at page 12, line 14 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Figure 29 is an example of a phage display vector, having SEQ ID NO:[[54]] 53, for use in accordance with the present invention. - -

Please amend the paragraph starting at page 12, line 16 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Figure 30 depicts the polynucleotide sequences of the V_L and V_H of MSPRO antibodies of the present invention SEQ ID NOS: [[61-91]]54-84. - -

Please amend the paragraph starting at page 14, line 16 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The molecule having the antigen-binding portion of an antibody according to the present invention can be used in a method for blocking the ligand-dependent activation and/or ligand independent (constitutive) activation of FGFR3. Preferred embodiments of such antibodies/molecules, obtained from an antibody library designated as HUCAL ~~HuCAL~~® (Human Combinatorial Antibody Library) clone, is presented in Table 1A with the unique V_H-CDR3 and V_L-CDR3 sequences given. - -

Please amend page 17 in the substitute specification filed June 7, 2004 as set forth in the following amendment:

- - MS-Pro-2-VL (SEQ ID NO: [[92]]85)

1 DIELTQPPSV SVAPGQTARI SCSGDALGDK YASWYQQKPG QAPVLVIYDD

51 SDRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQSY DYSADYVFGG

101 GTKLTVLGQ

corresponding to polynucleotide sequence having SEQ ID NO:[[74]] 67

MS-Pro-11-VL (SEQ ID NO: [[93]]86)

1 DIALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI

51 YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC QSHHFYEVFG

101 GGTKLTVLGQ

corresponding to polynucleotide sequence having SEQ ID NO:[[70]] 63

MS-PRO-12-VL (SEQ ID NO: [[94]]87)

1 DIELTQPPSV SVAPGQTARI SCSGDALGDK YASWYQQKPG QAPVLVIYDD

51 SDRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQSY DFDFAVFGGG

101 TKLTVLGQ

corresponding to polynucleotide sequence having SEQ ID NO:[[77]] 68

MS-Pro-21-VL (SEQ ID NO: [[95]]88)

1 DIVMTQSPDS LAVSLGERAT INCRSSQSVL YSSNNKNYLA WYQQKPGQPP

51 KLLIYWASTR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYCQQYDSI

101 PYTFGQGTKV EIKRT

corresponding to polynucleotide sequence having SEQ ID NO:[[67]] 60

MS-Pro-24-VL (SEQ ID NO: [[96]]89)

1 DIVLTQSPAT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY

51 GASSRATGVP ARFSGSGSGT DFTLTISSLE PEDFATYYCQ QMSNYPDTFG

101 QGTKVEIKRT

corresponding to polynucleotide sequence having SEQ ID NO:[[64]] 57

MS-Pro-26-VL (SEQ ID NO: [[97]]90)

1 DIALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI

51 YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC QSYDNNSDVV

101 FGGGTKLTVL GQ

corresponding to polynucleotide sequence having SEQ ID NO:[[71]] 64

MS-Pro-28-VL (SEQ ID NO: [[98]]91)

1 DIQMTQSPSS LSASVGDRVT ITCRASQGIS SYLAWYQQKP GKAPKLLIYA

51 ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFAVYYCFQ YGSIPPTFGQ

101 GTKVEIKRT

corresponding to polynucleotide sequence having SEQ ID NO:[[62]] 55

MS-Pro-29-VL (SEQ ID NO: [[99]]92)

1 DIVLTQSPAT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY

51 GASSRATGVP ARFSGSGSGT DFTLTISSLE PEDFATYYCQ QTNNAPVTFG

101 QGTKVEIKRT

corresponding to polynucleotide sequence having SEQ ID NO:[[65]] 58

MS-Pro-54-VL (SEQ ID NO: [[100]]93)

1 DIELTQPPSV SVAPGQTARI SCSGDALGDK YASWYQQKPG QAPVLVIYDD

51 SDRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQSY DYFKLVFGGG

101 TKLTVLGQ

corresponding to polynucleotide sequence having SEQ ID NO:[[73]] 66

MS-Pro-55-VL (SEQ ID NO: [[101]]94)--

Please amend page 18 in the substitute specification filed June 7, 2004 as set forth in the following amendment:

--1 DIALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI
51 YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC QSYDMYNYIV
101 FGGGTKLTVL GQ
corresponding to polynucleotide sequence having SEQ ID NO:[[69]] 62

MS-Pro-59-VL (SEQ ID NO: [[102]]95)
1 DIELTQPPSV SVAPGQTARI SCSGDALGDK YASWYQQKPG QAPVLVIYDD
51 SDRPSGIPER FSGSNSGNTA TLTISGTQAE DEADYYCQSY DGPDLWVFGG
101 GTKLTVLGQ
corresponding to polynucleotide sequence having SEQ ID NO:[[76]] 69

MS-Pro-2-VH (SEQ ID NO: [[103]]96)
1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW
51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARDF
101 LGYEFDYWGQ GTLVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[84]] 77

MS-Pro-11-VH (SEQ ID NO: [[104]]97)
1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW
51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARYY
101 GSSLYHYVFG GFIDYWGQGT LVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[85]] 78

MS-Pro-12-VH (SEQ ID NO: [[105]]98)
1 QVQLKESGPA LVKPTQTLTL TCTFSGFSLS TSGVGVGWIR QPPGKALEWL
51 ALIDWDDDKY YSTSLKTRLT ISKDTSKNQV VLTMTNMDPV DTATYYCARY
101 HSWYEMGYYG STVGYMFDYW GQGTLVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[89]] 82

MS-Pro-21-VH (SEQ ID NO: [[106]]99)

1 QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG

51 IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARDN

101 WFKPFSDVWG QGTLVTVSS

corresponding to polynucleotide sequence having SEQ ID NO:[[78]] 71

MS-Pro-24-VH (SEQ ID NO: [[107]]100)

1 QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG

51 IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARVN

101 HWTYTFDYWG QGTLVTVSS

corresponding to polynucleotide sequence having SEQ ID NO:[[79]] 72

MS-Pro-26-VH (SEQ ID NO: [[108]]101)

1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW

51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARGY

101 WYAYFTYINY GYFDNWGQGT LVTVSS

corresponding to polynucleotide sequence having SEQ ID NO:[[86]] 79

MS-Pro-28-VH (SEQ ID NO: [[109]]102)

1 QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG

51 IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARGG

101 GWVSHGYYYL FDLWGQGTLV TVSS

corresponding to polynucleotide sequence having SEQ ID NO:[[80]] 73

MS-Pro-29-VH (SEQ ID NO: [[110]]103)

1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW--

Please amend page 19, lines 1-21 in the substitute specification filed June 7, 2004 as set forth in the following amendment:

--51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARTW
101 QYSYFYYLDG GYYFDIWGQG TLVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[87]] 80

MS-Pro-54-VH (SEQ ID NO: [[111]]104)
1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW
51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARNM
101 AYTNYQYVNM PHFDYWGQGT LVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[82]] 75

MS-Pro-55-VH (SEQ ID NO: [[112]]105)
1 QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYYMHWVRQA PGQGLEWMGW
51 INPNSGGTNY AQKFQGRVTM TRDTSISTAY MELSSLRSED TAVYYCARSM
101 NSTMYWYLRR VLFDHWGQGT LVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[83]] 76

MS-Pro-59-VH (SEQ ID NO: [[113]]106)
1 QVQLQQSGPG LVKPSQTLSL TCAISGDSVS SNSAAWNWIR QSPGRGLEWL
51 GRTYYRSKWY NDYAVSVKSR ITINPDTSKN QFSLQLNSVT PEDTAVYYCA
101 RSYYPDFDYW GQGTLVTVSS
corresponding to polynucleotide sequence having SEQ ID NO:[[91]] 84 - -

Please amend the paragraph starting at page 19, line 23 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - In addition to sequencing of the clones, a series of biochemical assays were performed to determine affinity and specificity of the molecules to the respective receptors. Table 1C lists the affinity of the respective molecules to FGFR3 and FGFR1 as measured by BIACOREBIAcore®-and/or FACS. In a binding assay to FGFR3-expressing cells, the IC_{50} of the molecules was calculated (Example 6). Domain specificity was determined as described in

Example 8. The ligand-independent inhibition of FGFR3 (neutralizing activity) was determined as described in Example 10. Finally, the molecules were synthesized in a number of different formats including Fab, miniantibody (Fab-dHLX), IgG1, IgG4, IgG3 and as single chain Fv (scFv). - -

Please amend the page 20, line 6 in the substitute specification filed June 7, 2004 as set forth in the following:

- - BIACORE~~BIAcore~~® results for certain molecules - -

Please amend the paragraph starting at page 20, line 7 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The numbers in Table 1D represent the IC_{50}s of the dimeric dHLX format of certain binders (molecule with antigen binding site) in the FDCP-FGFR3 proliferation assay performed with FGF9. The numbers in parentheses are the IC_{50} of the monomeric Fabs in the same assay. Table 1E presents the K_D value for certain MSPRO molecules in miniantibody form, as determined in the BIACORE~~BIAcore~~® assay. - -

Please amend the paragraph starting at page 21, line 2 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Certain non-limiting embodiments of molecules according to the present invention that block constitutive (ligand-independent) activation of FGFR3 are referred to herein MSPRO2, MSPRO12 and MSPRO59 comprising V_H-CDR3 and V_L-CDR3 domains having SEQ ID NO:8 and SEQ ID NO:9; SEQ ID NO:12 and SEQ ID NO:13; and SEQ ID NO:24 and SEQ ID NO:25, respectively. The preferred, but non-limiting, embodiments of molecules according to the present invention that block ligand-dependent activation of FGFR3 are referred to herein MSPRO11, MSPRO21, MSPRO24, MSPRO26, MSPRO29, and MSPRO54 comprising VH-CDR3 and VL-CDR3 domains having SEQ ID NO:10 and SEQ ID NO:11; SEQ ID NO:14 and SEQ ID NO:15; SEQ ID NO:16 and SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:23 and SEQ ID NO:24, respectively. An antibody or a molecule of the present invention is said to have increased affinity for a RPTK if it binds a

soluble dimeric form of said RPTK with a K_D of less than about 50 nM, preferably less than about 30 nM and more preferably less than about 10 nM, as determined by the BIACOREBIAcore® chip assay for affinity, by a FACS-Scatchard analysis or other methods known in the art. - -

Please amend the paragraph starting at page 31, line 27 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The combined treatment of one or more of the molecules of the invention with an anti-neoplastic or anti-chemotherapeutic drug such as doxorubicin, cisplatin or taxol TAXOL® provides a more efficient treatment for inhibiting the growth of tumor cells than the use of the molecule by itself. In one embodiment, the pharmaceutical composition comprises the antibody and carrier with an anti-chemotherapeutic drug. - -

Please amend the paragraph starting at page 32, line 9 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The invention also provides isolated nucleic acid molecule that hybridizes under high stringency conditions to polynucleotides having SEQ ID NO:30 through SEQ ID NO:51 and SEQ ID NOS: 62, 64-65, 67, 69-71, 73-76 78-80, 82-87, 89-91 55, 57-58, 60, 62-64, 66-69, 71-73, 75-80, 82, 84 or the complement thereof. As used herein, highly stringent conditions are those which are tolerant of up to about 5-20% sequence divergence, preferably about 5-10%. Without limitation, examples of highly stringent (-10° C. below the calculated Tm of the hybrid) conditions use a wash solution of 0.1.times.SSC (standard saline citrate) and 0.5% SDS at the appropriate Ti below the calculated Tm of the hybrid. The ultimate stringency of the conditions is primarily due to the washing conditions, particularly if the hybridization conditions used are those which allow less stable hybrids to form along with stable hybrids. The wash conditions at higher stringency then remove the less stable hybrids. A common hybridization condition that can be used with the highly stringent to moderately stringent wash conditions described above is hybridization in a solution of 6xSSC (or 6xSSPE), 5x Denhardt's reagent, 0.5% SDS, 100 μg/ml

denatured, fragmented salmon sperm DNA at an appropriate incubation temperature Ti. See generally Sambrook et al.[[,]] (Molecular Cloning: A Laboratory Manual, 2d edition, Cold Spring Harbor Press (1989)) for suitable high stringency conditions. - -

Please amend the paragraph starting at page 38, line 6 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - To express this FGFR3 variant, 293E cells (EBNA virus transfected 293 cells) were transfected with the aforementioned plasmid, pCEP-hFR3$^{23\text{-}374}$TDhis, clones were identified and grown. Cell supernatants analyzed by Western blot with anti-His antibody demonstrated high expression of the soluble receptor. Supernatants from large scale preparations were then subjected to batch affinity purification with Ni-NTA beads and the tagged soluble receptor was eluted by a step gradient ranging from 20 mM to 500 mM imidazol. A sample from each elute was loaded onto a 7.5% SDS-PAGE and stained with GELCODE~~GelCode~~® (Pierce). In parallel, Western blot analysis was performed and analyzed with anti-His antibodies. SDS-PAGE (**FIG. 1**) and immunoblot (not shown) analyses demonstrated peak amounts of purified extracellular FGFR3 in the 2nd (2) 50 mM imidazol fraction. About 0.5 mg of pure protein was obtained following this single step purification. In Figure 1, T=total protein, D=dialysed protein, U=unbound fraction. - -

Please amend the paragraph starting at page 39, line 6 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Both FR3exFc and FR1exFc soluble receptors were demonstrated to be expressed to a high level in transiently transfected 293T cells (T-cell antigen infected human embryonic kidney 293 cells). The observation that both soluble receptors remain bound to heparin-coated wells even following extensive washes led the laboratory of the present inventors to try to purify the proteins with the commercial HEPARIN-SEPHAROSE~~Heparin-Sepharose~~® resin (Pharmacia). One hundred ml volume supernatants, harvested 48 hours post-transfection with either FR3exFc or FR1exFc coding plasmids, were incubated overnight at 4 °C. with 1 ml HEPARIN-SEPHAROSE~~Heparin-Sepharose~~® resin. The resin was washed and then subjected to PBS

supplemented with increasing concentration of NaCl. Aliquots of each fraction were analyzed by 7.5% SDS-PAGE stained with GELCODE~~GelCode~~® (Pierce) demonstrating a purification profile of more than 90% homogeneity and a peak elution at 400 mM NaCl for FR3exFc (FIG. 3; T=total protein, U=unbound fraction, W=wash). In contrast, FR1exFc was hardly retained on the resin. This result was confirmed by Western analysis of the same fractions with anti-FGFR1ex antibodies demonstrating that most of FR1 exFc is in the unbound fraction (not shown). - -

Please amend the paragraph starting at page 40, line 3 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The screening strategies to identify Fabs from the Human Combinatorial Antibody Library (HUCAL~~HuCAL~~®, developed at MorphoSys, Munich, Germany and disclosed in WO 97/08320, U.S. Pat. No. 6,300,064, and Knappik et al., (2000), the entire contents of which are incorporated herein by reference, using soluble dimeric forms of the extracellular domain of the FGFR3 receptor are shown in Table 2. - -

Please amend the paragraph starting at page 41, line 6 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Figure 30 displays the polynucleotide sequences of the specific V_L and V_H domains of MSPRO2 (SEQ ID NO:[[74]] 67 and [[84]] 77); MSPRO11 (SEQ ID NO:[[70]] 63 and [[85]] 78); MSPRO12 (SEQ ID NO:[[75]] 68 and [[89]] 82); MSPRO21 (SEQ ID NO:[[67]] 60 and [[78]] 71); MSPRO24 (SEQ ID NO:[[64]] 57 AND [[79]] 72); MSPRO26 (SEQ ID NO:[[71]] 64 AND [[86]] 79); MSPRO28 (SEQ ID NO:[[62]] 55 AND [[80]] 73); MSPRO29 (SEQ ID NO:[[65]] 58 AND [[87]] 80); MSPRO54 (SEQ ID NO:[[73]] 66 AND [[82]] 75); MSPRO55 (SEQ ID NO:[[69]] 62 AND [[83]] 76); and MSPRO59 (SEQ ID NO:[[76]] 69 AND [[91]] 84). The sequences include the framework domains 1-4 and the CDR domains 1-3. SEQ ID NO:[[61]] 54, SEQ ID NO:[[63]] 56, SEQ ID NO:[[66]] 59, SEQ ID NO:[[68]] 61, and SEQ ID NO:[[73]] 65 denote herein the polynucleotide sequences of the parent V_L (kappa or lambda) strands. SEQ ID NO:[[77]] 70, SEQ ID NO:[[81]] 74, SEQ ID NO:[[88]] 81 and SEQ ID NO:[[90]] 83 denote herein the polynucleotide sequences of the V_H parent strands. - -

Please amend the paragraph starting at page 41, line 24 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - MAXISORP~~MaxiSorp~~® ELISA plates were coated with 100 µl anti-human Fc (10 µg/ml) in bicarbonate overnight at 4° C. Wells were washed five consecutive times with a PBS solution containing 0.1% Tween 20 (PBST). The well surface was blocked with 250 µl PBST+3% BSA (blocking solution) for 1 hour at 37° C. This was followed by capturing 1 µg of FGFR/Fc for 1 hour at room temperature. To assess the antibody binding to the captured FGFR/Fc, 1 µg each of the tested Fabs was incubated in 100 µl blocking solution per well 1 hour at room temperature. Wells were washed 5 times with PBST. Reaction was initiated with the addition of 100 µl of 0.8 µg/ml goat anti-human Fab-HRP (horseradish peroxidase) diluted in blocking solution, subsequently washed and detected with TMB substrate (Pierce). The absorbance was measured at 450 nm. A comparison of ELISA analyses done in both laboratories, Prochon and MorphoSys, is presented in Figure 27 and in Table 4. - -

Please amend the paragraph starting at page 42, line 9 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The affinity measurements were performed by BIACORE~~BIAcore~~® analysis according to the standard procedure recommended by the supplier (Pharmacia). The anti-Fc antibody was coupled via the EDC/NHS chemistry to the chip and subsequently FGFR3 was captured. The Fabs of the invention were then bound to this surface. - -

Please amend the paragraph starting at page 43, line 3 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Table 5 shows a comparison of affinities of Fabs candidates to FGFR3 as determined by BIACORE~~BIAcore~~® and by FACS-scatchard. - -

Please amend the paragraph starting at page 43, line 9 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Table 1E (in the Detailed Description, *vide supra*) shows the affinity as determined by BIACOREBIAcore® for the Fab candidates shown in Table 5 converted into the Fab mini-antibody format, Fab-dHLX-MH, where a dimer of the Fab monomer is produced after insertion into an expression vector as a fusion protein. - -

Please amend the paragraph starting at page 48, line 1 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - The protein content was determined by Bradford or DC protein assay (Bio-Rad, cat# 500-0116) following manufacture instructions. Total protein aliquots, supplemented with 1/5 volume of 5Xsample buffer, were boiled for 5 minutes and stored at -20° C. until ready to load on gel. In parallel an immunoprecipitation (IP) assay was performed, 10 µl anti-FGFR3 antibodies were added to the rest of the lysates and incubated for 4 hours at 4° C. Twenty (20) ul protein A-SEPHAROSESepharose® was added and incubated for 1 hour at 4° C. with continuous shaking. Afterwards, the mixture was microcentrifuged 15 seconds, and the fluid was aspirated, carefully leaving a volume of ~30 µl above the beads. The beads were washed 3 times with 1 ml lysis buffer. At this step, the protease inhibitor mix was omitted from the buffer. - -

Please amend the paragraph starting at page 48, line 26 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - BIACOREBIAcore® and proliferation analyses showed that among the new Fabs, MSPRO54 is highly cross reactive with FGFR1. To further test the cross reactivity of the new Fabs, RCJ cells expressing either FGFR3ach (RCJ-M14; M14 on FIG. 9A) FGFR3 wild type (W 11 on FIG. 9B), FGFR1 (R1-1 on FIG. 9C) or FGFR2 (R2-2 on FIG. 9D) were incubated with increasing amount of a control antibody LY6.3, MSPRO29, 54 and 59 for one hour. FGF9 was added for 5 minutes and cell lysates were analyzed by Western blot for ERK activation (phosphorylated ERK; pERK) **(~~Figs. 9A-9D~~) (FIGS. 9A, 9B, 9C and 9D)**. Furthermore, MSPRO13 was able to block FGFR1 activation while none of the Fabs blocked FGFR2

activation. ~~Figures 9A-9D~~ **FIGS. 9A, 9B, 9C and 9D** show the results of several Fabs, at different mg concentrations, on RCJ expressing wildtype FGFR3 or the different FGFR types. MSPRO29 appeared as the best FGFR3 blocker and was also effective in blocking FGFR1 (FIG. 9c); however, MSPRO54 was the most effective Fab against FGFR1. None of the Fabs significantly inhibited FGFR2 activity. There are only a few amino acid residues within the third Ig domain that are shared by FGFR3 and FGFR1 but not by FGFR2. Making mutants at these sites should clarify their role in Fab-receptor binding. - -

Please amend the paragraph starting at page 50, line 9 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - To determine the effect of iodination on Fab activity, 50 μg of MSPRO29 was first labeled with cold iodine using Pierce IodoGen coated tubes. The process was carried out either without iodine, with 0.04 mM NaI (low I) or with 1 mM NaI (high I). MSPRO29 was then purified through a SEPHADEX~~Sephadex~~® G-50 column. The ability of the modified Fab to bind FGFR3 was determined by ELISA. MAXISORP~~MaxiSorp~~® wells were coated with anti-human Fc. FGFR3/Fc was then anchored to the wells. In parallel, a similar set of wells was left in blocking buffer only (no FR3/Fc, hatched bars). The unmodified (no I) or the modified MSPRO29 (low or high, 2 G-50 fractions each, 1 and 2) were added at approximately 5 μg/well and binding was measured with anti-human Fab. Fresh MSPRO29 and buffer alone were included as controls (FIG. 14: FGFR3/Fc, checkered bars; no FGFR3/Fc, hatched bars). MS-PRO29 was labeled with 1 mCi ^{125}I. The specific activity of the Fab was 17 μCi/μg. - -

Please amend the paragraph starting at page 51, line 2 in the substitute specification filed June 7, 2004 as set forth in the following amended paragraph:

- - Femora prepared from newborn mice were incubated with 2 μg ^{125}I-MSPRO29 (17 μCi/μg) or ^{125}I-Ly6.3 (20 μCi/μg) for 1, 3 or 5 days in culture. Then, sections were processed for radiomicroscopy. After 3 days in culture, MSPRO29 was predominantly visualized at the higher hypertrophic zone and to a lesser extent at the secondary ossification region (~~FIGS. 16A-16F~~ **FIGS. 16A, 16B, 16C, 16D, 16E and 16F**). Hematoxylin-eosin staining of growth plate treated with radiolabeled MSPRO29 or Ly6.3 (**FIGS. 16A** and **16D**, respectively) x100 magnification.

Radiomicroscopic sections of growth plate treated with radiolabeled MSPRO29 or Ly6.3 (**FIGS. 16B** and **16E**) at X100 magnification. **FIGS. 16C** and **16F** are the same as **FIGS. 16B** and **16E** but at x400 magnification. The arrows in **FIGS. 16B** and **16C** indicate the location of the specific binding of the radiolabelled MSPRO29 to the higher hypertrophic zone of the growth plate. - -

Please replace TABLE 1F starting on page 21 of the substitute specification with the following Table 1F:

TABLE 1F:

Peptide pairs
Fragment

antibody #	V heavy chain CDR3	V light chain CDR3	V heavy chain	V light chain
MSPRO2	SEQ ID NO: 8	SEQ ID NO: 9	SEQ ID NO: 96	SEQ ID NO: 85
MSPRO12	SEQ ID NO: 12	SEQ ID NO: 13	SEQ ID NO: 98	SEQ ID NO: 87
MSPRO59	SEQ ID NO: 24	SEQ ID NO: 25	SEQ ID NO: 106	SEQ ID NO: 95
MSPRO11	SEQ ID NO: 10	SEQ ID NO: 11	SEQ ID NO: 97	SEQ ID NO: 86
MSPRO21	SEQ ID NO: 14	SEQ ID NO: 15	SEQ ID NO: 99	SEQ ID NO: 88
MSPRO24	SEQ ID NO: 16	SEQ ID NO: 17	SEQ ID NO: 100	SEQ ID NO: 89
MSPRO26	SEQ ID NO: 18	SEQ ID NO: 19	SEQ ID NO: 101	SEQ ID NO: 90
MSPRO28	SEQ ID NO: 26	SEQ ID NO: 27	SEQ ID NO: 102	SEQ ID NO: 91
MSPRO29	SEQ ID NO: 20	SEQ ID NO: 21	SEQ ID NO: 103	SEQ ID NO: 92
MSPRO54	SEQ ID NO: 22	SEQ ID NO: 23	SEQ ID NO: 104	SEQ ID NO: 93
MSPRO55	SEQ ID NO: 28	SEQ ID NO: 29	SEQ ID NO: 105	SEQ ID NO: 94

Please replace TABLE 1G starting on page 22 of the substitute specification with the following Table 1G:

TABLE 1G:

Nucleotide pairs
fragment

antibody #	V heavy chain CDR3	V light chain CDR3	V heavy chain	V light chain
MSPRO2	SEQ ID NO: 30	SEQ ID NO: 31	SEQ ID NO: 77	SEQ ID NO: 67
MSPRO12	SEQ ID NO: 34	SEQ ID NO: 35	SEQ ID NO: 82	SEQ ID NO: 68
MSPRO59	SEQ ID NO: 50	SEQ ID NO: 51	SEQ ID NO: 84	SEQ ID NO: 69

MSPRO11	SEQ ID NO: 32	SEQ ID NO: 33	SEQ ID NO: 78	SEQ ID NO: 63
MSPRO21	SEQ ID NO: 36	SEQ ID NO: 37	SEQ ID NO: 71	SEQ ID NO: 60
MSPRO24	SEQ ID NO: 38	SEQ ID NO: 39	SEQ ID NO: 72	SEQ ID NO: 57
MSPRO26	SEQ ID NO: 40	SEQ ID NO: 41	SEQ ID NO: 79	SEQ ID NO: 64
MSPRO28	SEQ ID NO: 42	SEQ ID NO: 43	SEQ ID NO: 73	SEQ ID NO: 55
MSPRO29	SEQ ID NO: 44	SEQ ID NO: 45	SEQ ID NO: 80	SEQ ID NO: 58
MSPRO54	SEQ ID NO: 46	SEQ ID NO: 47	SEQ ID NO: 75	SEQ ID NO: 66
MSPRO55	SEQ ID NO: 48	SEQ ID NO: 49	SEQ ID NO: 76	SEQ ID NO: 62

Examiner's Statement of Reasons for Allowance

6. The following is an examiner's statement of reasons for allowance:

The prior art does not teach or fairly suggest antibodies that specifically bind the extracellular domain of the human fibroblast growth factor receptor 3 (FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO:1 wherein said antibody or said antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:95 or antibodies that specifically bind the extracellular domain of the human fibroblast growth factor receptor 3 (FGFR3 polypeptide comprising the amino acid sequence of SEQ ID NO:1 wherein said antibody or said antigen-binding fragment thereof comprises a heavy chain variable region comprising the 3 CDRs of the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the 3 CDRs of the amino acid sequence of SEQ ID NO:95.

Written support for new claims 50-52 is found throughout the specification as originally filed; see, e.g., pages 23-25, which discloses CDR grafting technologies to make antibodies and that the heavy and light chain each comprise 3 CDRs and Figure 30, which specifically identifies the nucleotide sequences encoding each of the 6 CDRS of the heavy and light chains of antibody MSPRO59 (i.e., an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:95 (see Table 1F)). Based on this disclosure one of skill in the art would be able to

immediately envision the amino acid sequences the 6 CDRs of MSPRO59, which would permit the claimed antibody to be made without undue or unreasonable experimentation; thus, the artisan would reasonably conclude that Applicant was in possession of the genus of antibodies that specifically bind the extracellular domain of the human fibroblast growth factor receptor 3 (FGFR3) polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein said antibody or said antigen-binding fragment thereof comprises a heavy chain variable region comprising the 3 CDRs of the amino acid sequence of SEQ ID NO:106 and a light chain variable region comprising the 3 CDRs of the amino acid sequence of SEQ ID NO:95.

7. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Information Disclosure Statement

8. The references cited in the information disclosure statement filed on September 3, 2008, have been considered. The Trudel et al reference was crossed out because this reference was previously made of record by the Examiner on July 25, 2007.

Conclusion

9. Claims 1, 10, 31 and 50-52 have been allowed.

10. Claims 10, 31 and 50-52 have been renumbered as claims 2, 3 and 4-6, respectively.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
September 12, 2008